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Tumor localization and other factors affecting prognosis in elderly patients with colon cancer

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Abstract

Aim: In this study, we aimed to evaluate tumor localization, clinicopathological features, and response to treatment in elderly patients with colon cancer and determine their prognostic significance and effect on overall survival (OS).

Material and Methods: Data were retrospectively collected by screening the files of 84 elderly (>75 years old) patients with colon cancer followed up in our hospital between 2010 and 2022. According to tumor localization, the cases were divided into the right colon and left colon cancer groups. The patients' demographic data (age, gender), clinicopathological features, tumor type, grade, size, and localization, and the presence of metastases were evaluated. The presence of K-RAS and BRAF, tumor stage, histology, tumor localization, and whether chemotherapy was applied were evaluated using multivariate and univariate analyses to determine their relationship with OS and prognosis.

Results: The study included a total of 84 patients, of whom 42 (50%) were male and 42 (50%) were female. The tumor was located in the right colon in 28 (33.3%) patients and in the left colon in 56 (66.7%) patients. The median mean age was 81 (77-91) years. Thirty-two (38.1%) patients were found to have the K-RAS mutant type, and 52 (61.9%) patients had the K-RAS wild-type. Five (6%) patients had the BRAF mutant type. OS and prognosis were worse in right colon tumors, in patients with RAS mutants, in those not receiving chemotherapy, and in those with advanced-stage tumors.

Discussion: Among the elderly patients with colon cancer, tumor localization in the right colon, the presence of RAS mutants, not having received chemotherapy, and the presence of advanced tumors were evaluated as poor prognostic factors. In the geriatric population, patient-tailored treatment should be planned with a multidisciplinary approach by considering the individual requirement of each patient.

Keywords

Elderly Patient, Colon Cancer, Tumor Localization, Prognosis

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Introduction

Colorectal cancer (CRC) has high mortality in advanced stages and is globally the third most common cancer with an incidence of 9.8% and a mortality rate of 9.2% [1,2]. CRC does not present with a uniform tumor, and its pathogenesis depends on the anatomical localization of the tumor. Laterality is an important topic of discussion in CRC. According to the American Cancer Society data, the incidence of left colon cancer (LCC) (51%) is higher than that of right colon cancer (RCC) (42%) [3]. There are also differences in clinicopathological and genetic features between right and left colon cancer cases [1,3]. Clinicopathologically, iron deficiency anemia and exophytic-polypoid lesions growing into the colon lumen are seen in RCC. It is progressive, poorly differentiated, and associated with different molecular biological tumor patterns. LCC involves infiltrating lesions that surround the lumen and cause obstruction [4,7]. Genetically, mucinous histology and high microsatellite instability (MSI-high tumors) are frequently seen in RCC, while K-RAS, APC, p53, N-RAS, and epidermal growth factor receptor (EGFR) gene expression and HER2-neu amplifications including chromosomal instability (CIN) are more commonly observed in LCC. Of all CRC cases, 75-80% develop via the traditional CIN pathway. Many factors, such as patient age, tumor localization, molecular characteristics, and patient preferences should be considered in the selection of appropriate treatment. Advanced age and tumor localization are particularly important factors. Previously, studies have been conducted to compare epidemiological, pathological, and molecular characteristics of patients with colon cancer according to tumor localization. However, the geriatric age group has specific oncological, clinicopathological, and molecular features; therefore, it is necessary to evaluate this patient population separately. Based on this idea, we conducted the current study to evaluate the relationship of tumor localization, clinicopathological features, and treatment response with survival and prognosis in elderly patients with colon cancer.

Material and Methods

Data were retrospectively collected by screening the files of 971 patients diagnosed with colon cancer followed up at Manisa City Hospital between 2010 and 2022. Patients aged >75 years were included in the study. Of the 84 screened files, 77 were found to have complete data and were statistically evaluated. According to tumor localization, the cases were divided into the RCC and LCC groups. According to tumor localization, the RCC cases were evaluated as cecum/appendix, ascending colon, hepatic flexure, and proximal transverse colon (proximal two-thirds of the transverse colon), and the LCC cases as distal transverse colon (distal one-third of the transverse colon), splenic flexure, and descending and sigmoid colon. Patients with rectosigmoid and rectal cancer were not included in the study. Colonoscopy was performed in all the patients, and pathological evaluation was undertaken by biopsy. The performance status of the patients was evaluated using the Eastern Cooperative Oncology Group (ECOG) score. The tumor-node-metastasis (TNM) stage, pT stage, pN stage, and pM stage were classified according to the American Joint Committee on Cancer (AJCC, 7th edition). Lymph node metastasis, distant metastasis, tumor stage, perineural invasion (PNI), and lymphovascular invasion (LVI) were also assessed. The patients' demographic data (age, gender) and presence of RAS and BRAF mutations were recorded. The presence of K-RAS and BRAF, tumor stage, histology, tumor localization, and chemotherapy treatment were further analyzed with the multivariate and univariate analyses to determine their relationship with overall survival (OS) and prognosis. OS was defined as the time from diagnosis to mortality. The study was conducted in accor¬dance with the Declaration of Helsinki and the study protocol was approved by Celal Bayar University Medical School Health Sciences Ethics Committee (Date: 29/12/2021; No: 2021/ 20.478.486 /1113).

Statistical Analysis

Descriptive statistics were presented as numbers and percentages for categorical variables, and median, minimum, maximum, and mean values with standard deviation for numerical variables. Visual (histogram) and analytical methods (Kolmogorov-Smirnov/Shapiro-Wilk test) were used to determine the distribution of variables. Survival curves were obtained using the Kaplan-Meier analysis. Variables found to be significant in the univariate analysis were further analyzed with the Cox regression method. The prognostic value of clinicopathological features, the presence of RAS and BRAF, tumor localization, and chemotherapy response was investigated with the multivariate analyses, and OS time was calculated. The Statistical Package for the Social Sciences (SPSS) v. 21 software and R software were used to perform statistical analyses. $P < 0.05$ was considered statistically significant.

Ethical Approval

Ethics Committee approval for the study was obtained.

Results

The study included a total of 84 patients, of whom 42 (50%) were male and 42 (50%) were female. Of the patients, 76 (90.5%) had adenocarcinoma, 6 (7.1%) had mucinous carcinoma, and two (2.4%) had signet ring cell carcinoma. Seventy-six (90.5%) patients died, and eight (9.5%) patients were still alive at the last follow-up. The tumor was located in the right colon in 28 (33.3%) patients and left colon in 56 (66.7%). At the time of diagnosis, 17 (20.2%) cases were identified as stage 1-3 and 67 (79.8%) as stage 4. LVI was found in 75% of the patients and PNI in 72.6%. The median age was 81 (77-91) years. Thirty-two (38.1%) patients were found to have the K-RAS mutant type, 52 (61.9%) had the K-RAS wild type, and five (6%) had the BRAF mutant type. Univariate and multivariate analyses were undertaken to evaluate the effect of the presence of K-RAS, presence of BRAF, tumor stage, histology, tumor location, and treatment response on OS and prognosis (Tables 1, 2). Seventy-seven (91.7%) patients received one of the treatments of bevacizumab, cetuximab or panitumumab during chemotherapy. Seven (8.3%) patients received no treatment. Treatment could not be applied in these patients due to poor ECOG performance scores, comorbid diseases, or refusal of their relatives from treatment. The median follow-up time was 13.7 months. The median survival time was 16 [95% confidence interval (CI): 11.76-20.24] months. The one-year, two-year, and three-year survival rates were determined as 50, 17, and 6%, respectively. The median survival time was 10 (95% CI: 5.60-14.00) months

in the RCC group and 18 (95% CI: 13.72-22.28) months in the LCC group (p = 0.006). When evaluated according to the mutant types, the median survival time was 20 (95% CI: 10.99-29.01) months for the RAS wild type and 14 (95% CI: 9.55-18.46) months for the RAS mutant type (p = 0.034). The relationship of K-RAS, chemotherapy status, tumor localization, and tumor stage with OS was analyzed using the Kaplan-Meier method (Figures 1-3).

Discussion

The incidence of colon cancer is increasing as a result of the increase in life expectancy and growing elderly population. In CRC, the median age at the time of diagnosis is 69 years, and 70% percent of CRC cases are seen at the age of 65 and over. CRC tends to be at a more advanced stage and has a worse diagnosis in the elderly. The elderly population is more fragile and has lower functional capacity, and therefore has a higher risk of colon cancer. In the geriatric group, patient management and prognostic evaluation are important due to various reasons, such as the presence of comorbid diseases, poor performance, patients refusing treatment, chemotherapy-related side effects, drug-related toxicity, and immune system deficiency. In this study, it was shown that RCC had a worse prognosis and lower survival in elderly patients with colon

Table 1. Demographic and histopathological data

Parameter		n (%)
Gender	Male	42 (50%)
	Female	42 (50%)
Histology	Adenocarcinoma	76 (90.5%)
	Mucinous carcinoma	6 (7.1%)
	Signet ring cell carcinoma	2 (2.4%)
Stage at diagnosis	Stages 1-3	17 (20.2%)
	Stage 4	67 (79.8%)
Grade	1-2	64 (76.2%)
	3	20 (23.8%)
ECOG performance score	2	65 (77.4%)
	3	19 (22.6%)
Lymphovascular invasion	Positive	63 (75%)
Perineural invasion	Positive	61 (72.6%)
Liver metastasectomy	Present	2 (2.4%)
Tumor side	Right	28 (33.3%)
	Left	56 (66.7%)
BRAF mutant	Present	5 (6%)
RAS mutant	Present	32 (38.1%)

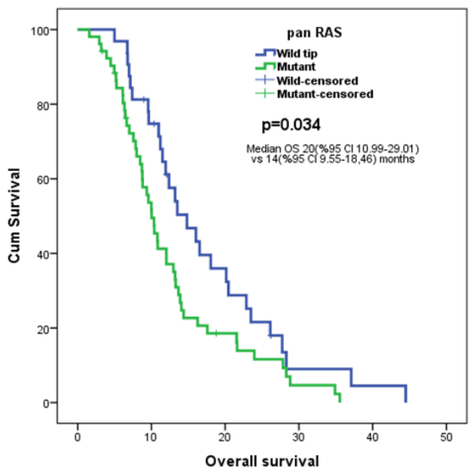

Figure 1. Kaplan-Meier curves of the relationship between Pan RAS and overall survival (OS). (Median OS: 20 (95% CI: 10.99-29.01) vs 14 (95% CI: 9.55-18.46) months)

Table 2. Results of the univariate and multivariate analyses of factors affecting overall survival in colon cancer

	Univariate Analysis (HR, 95% CI)	P value	Multivariate Analysis (HR, 95% CI)	P value
Age	1.12 (1.03-1.23)	0.012	1.09 (0.99-1.19)	0.088
Gender	-0.9 (0.57-1.40)	0.66		
Tumor stage at diagnosis	3.34 (1.75-6.38)	<0.001	2,45 81.28-4.69)	0.007
Histology	-0.58 (0.11-3.22)	0.53		
Tumor grade	1.76 (1.06-2.98)	0.03	1.75 (1.02-3.00)	0.041
Tumor localization	1.99 (1.21-3.56)	0.006	2.23 (1.13- 4.40)	0.02
BRAF mutant	1.06 (0.99-1.14)	0.11		
RAS mutant	1.68 (1.04-2.71)	0.034	2.01 (1.17-3.42)	0.01
Treatment status	1.74 (1.74-10.77)	0.002	8.33 (3.04-22.86)	<0.001

HR: hazard ratio, CI: confidence interval

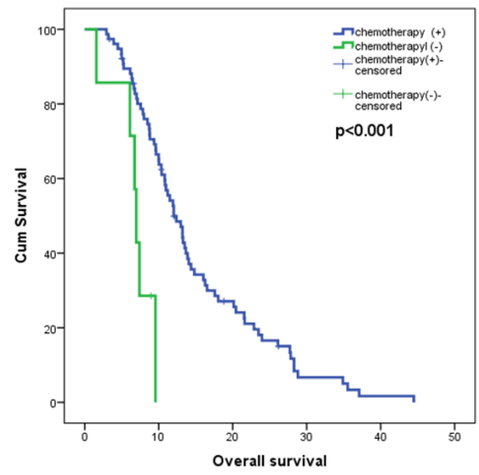

Figure 2. Kaplan-Meier curves of the relationship between chemotherapy status and overall survival (OS)

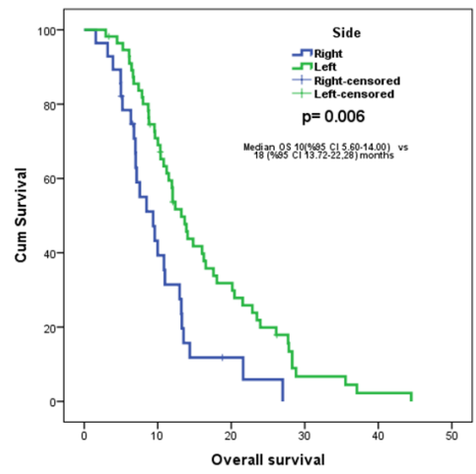

Figure 3. Kaplan-Meier curves of the relationship between tumor localization and overall survival (OS)

cancer. CRC is a heterogeneous disease in terms of histological type, tumor stage, and treatment response. This heterogeneity is caused by genetic, etiological, environmental and microbiota-related factors [8,10]. Bufill was the first to identify separate biological pathways for the development of RCC and LCC in 1990 [11]. According to the primary tumor localization (right colon/left colon) in colon cancer, there are differences in embryological origin and anatomical, histopathological, genetic, and immunological characteristics. During embryological development, a right colon tumor (cecum, ascending colon, and proximal 2/3 of transverse colon) originates from the midgut, while a left colon tumor (distal 1/3 of transverse colon, descending colon, and sigmoid colon) originates from the hindgut. Differences in mucosal immunology caused by variations in gut microbiota are also effective in this process. This can explain different molecular and biological tumor patterns [12]. In our study, tumors were located in the left colon in 56 (66.7%) patients. The K-RAS mutant type was detected in 32 (38.1%) patients6 and the wild-type K-RAS mutant in 52 (61.9%). It was also determined that the RCC and RAS-mutant tumors had a worse prognosis. Previous studies in the literature have shown that patients with LCC have a better prognosis and OS than those with RCC. In addition, the prognostic importance of K-RAS, N-RAS, and BRAF mutations has been demonstrated in recent years [13,17]. In a study by Venook et al., wild-type metastatic LCC was shown to result in better OS and progression-free survival compared to RCC. In another study, Schrag et al. reported that patients with right-sided stage III-IV CRC had a worse prognosis than those with left-sided CRC [18,19]. Weiss et al. noted that stage III LCC had a better prognosis but found no significant difference in mortality rates and any of the tumor stages in between RCC and LCC [20]. In a meta-analysis covering 66 studies, Petrelli et al. reported that tumor localization had significant prognostic value, and there was an 18% increase in the risk of mortality in patients with right-sided cancer [21]. Hiroko Nakagawa-Senda et al. observed that the survival rate for right-sided colon cancer was lower in the Japanese population [22]. In the current study, 67 (79.8%) patients had stage 4 and metastatic cancer at the time of diagnosis, and 17 (20.2%) had stage 1-3 cancer and developed recurrence and metastasis later. We determined that the prognosis was worse in advanced stage and metastatic cases at the time of diagnosis. The prognosis and mean survival were better in those who received treatment and had a low tumor stage. Advanced stage, presence of metastasis, and subsequent recurrence were associated with a poor prognosis. The tumor progresses more slowly in the elderly, but there is a higher probability of patients not accepting or tolerating treatment and a greater risk of side effects due to comorbidities, which places physicians in a difficult situation during the treatment phase. Therefore, we consider that treatment should be provided to elderly patients with a good ECOG performance score. The retrospective and single-center design and limited number of patients can be regarded as limiting factors for this study. In addition, since patients with rectal cancer were not included in the sample, a comparison could not be made. Larger studies are needed to elucidate the underlying mechanism of CRC in elderly patients.

Conclusion

CRC is not one type of disease but behaves like two different diseases in the same organ. Age and anatomical localization significantly affect tumor behavior, molecular and immunological features, and prognosis. In this study, RCC was found to have a worse prognosis in the elderly. More advanced stage, large tumor sizes, and poorly differentiated tumors were detected in the elderly patient with colon cancer. It was also determined that the prognosis was poorer in the patients with RAS mutants, in those who had not received chemotherapy, and those with advanced-stage tumors. Especially in elderly patients, the patient approach should be evaluated in a different category due to the presence of comorbid diseases, such as diabetes, patients' refusal of treatment, inability to administer adjuvant chemotherapy due to its side effects, functional losses, and limited life expectancy. In the elderly, screening procedures, treatment methods, and follow-up programs should be established according to tumor localization. In the follow-up of these patients, there is a need for individualized treatment with a multidisciplinary approach.

Scientific Responsibility Statement

The authors declare that they are responsible for the article's scientific content including study design, data collection, analysis and interpretation, writing, some of the main line, or all of the preparation and scientific review of the contents and approval of the final version of the article.

Animal and human rights statement

All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

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Conflict of interest

The authors declare no conflict of interest.

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